EXPRESS MAIL NO. EM511114339US

PATENT
PC9058JTL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE #5

IN RE U.S. PATENT NO. 4,264,500	
ISSUED: APRIL 28, 1981	
TO: WILLY ZWAHLEN	
FOR: PROCESS OF MAKING 6-CHLORO-α-METHYL-CARBAZOLE-2-ACETIC ACID	
FROM: SERIAL NO. 125,529	
OF: FEBRUARY 28, 1980	

Assistant Commissioner for Patents
Box Patent Extension
Washington, DC 20231

Sir:

CERTIFICATION

I hereby certify that attached hereto is a duplicate copy of the application papers of PFIZER INC., dated December 20, 1996, for extension of the term of United States Patent No. 4,246,500 under 35 U.S.C. §156.

Respectfully submitted,

Date: December 20, 1996

J. Trevor Lumb

J. Trevor Lumb
Reg. No. 28,567
Tel.: (212) 573-2521

Pfizer Inc.
Patent Department
235 East 42nd Street
New York, New York 10017-5755

official

EXPRESS MAIL NO. EM511114339US

PATENT
PC9058JTL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RECEIVED
DEC 20 1996
PATENT EXTENSION
A/C PATENTS

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Washington, DC 20231

Sir:

DECLARATION ACCOMPANYING APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

I, J. TREVOR LUMB, declare as follows.

1. I am a patent attorney. I am a member of the Bar of the State of New York and I am authorized to practice before the Patent and Trademark Office, Registration No. 28,567.

2. I am employed by PFIZER INC., a corporation of Delaware, having a place of business at 235 East 42nd Street, New York, NY 10017. PFIZER INC. is the owner of record of United States Patent No. 4,264,500.

3. I have general authority from PFIZER INC. to act on its behalf in patent matters.

4. I have reviewed and I understand the contents of the application of PFIZER INC., dated December 20, 1996, which is being submitted herewith for extension of the term of United States Patent No. 4,264,500 under 35 U.S.C. §156 and 37 C.F.R. §1.730.

5. I believe that United States Patent No. 4,264,500 is subject to extension pursuant to 37 C.F.R. §1.710.

6. I believe that the length of extension of term of United States Patent No. 4,264,500 which is being claimed by PFIZER INC. is justified under 35 U.S.C. §156 and the applicable regulations.

7. I believe that the patent for which extension is being sought meets the conditions for extension of the term of the patent as set forth in 37 C.F.R. §1.720.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application being submitted herewith or any extension of patent term granted thereon.

Signed this 20th day of December, 1996, at New York, New York.

J. Trevor Lumb

J. Trevor Lumb
Reg. No. 28,567
Tel.: (212) 573-2521

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Patent Department
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Assistant Commissioner for Patents
Box Patent Extension
Washington, DC 20231

Sir:

TRANSMITTAL OF APPLICATION FOR
EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Transmitted herewith are the application papers of PFIZER INC., dated December 20, 1996, for extension of the term of United States Patent No. 4,264,500 under 35 U.S.C. §156, together with a duplicate of the papers thereof, certified as such.

Please charge the sum of $1,090.00 to Deposit Account No. 16-1445. Please also charge any additional fees which may be required by the filing of this application for extension of patent term, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully submitted,
PFIZER INC.

Date: December 20, 1996

By: J. Trevor Lumb

J. Trevor Lumb
Reg. No. 28,567
Tel.: (212) 573-2521

Pfizer Inc.
Patent Department
235 East 42nd Street
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Sir:

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Respectfully submitted,
PFIZER INC.

Date: December 20, 1996

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Respectfully submitted,
PFIZER INC.

Date: December 20, 1996

By: J. Trevor Lumb

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Reg. No. 28,567
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Patent Department
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Assistant Commissioner for Patents
Box Patent Extension
Washington, DC 20231

Sir:

APPLICATION FOR EXTENSION OF THE TERM OF UNITED STATES PATENT NO. 4,264,500 UNDER 35 U.S.C. §156

Your applicant, PFIZER INC., a corporation organized and existing under the laws of the State of Delaware, and having a place of business at 235 East 42nd Street, New York, NY 10017, U.S.A., represents that it is the owner of the entire right, title and interest in and to Letters Patent of the United States No. 4,264,500, granted to WILLY ZWAHLEN on the 28th day of April 1981, for PROCESS OF MAKING 6-CHLORO-∝-METHYL-CARBAZOLE-2-ACETIC ACID, by virtue of an assignment, recorded in the United States Patent and Trademark Office on the 25th day of January, 1996, at Reel 7773, Frame 0646.

Pursuant to the provisions of 37 C.F.R. §1.730, your applicant hereby applies for an extension of the term of U.S. Patent No. 4,264,500 under 35 U.S.C. §156 of three (3) years, based on the materials set forth herein and in the accompanying papers.

PART I: THE REQUIREMENTS OF 37 C.F.R. §1.740(a)

In the materials in this Part, numbered paragraphs (1)-(17) correspond to paragraphs (1)-(17) of 37 C.F.R. §1.740(a).

(1) The approved product is RIMADYL Caplets ("RIMADYL"), which is further identified as follows.

Chemical Names

6-Chloro-∝-methyl-carbazole-2-acetic acid or

9H-Carbazole-2-acetic acid, 6-chloro-∝-methyl

Generic Name

Carprofen

Molecular Formula

$C_{15}H_{12}ClNO_2$

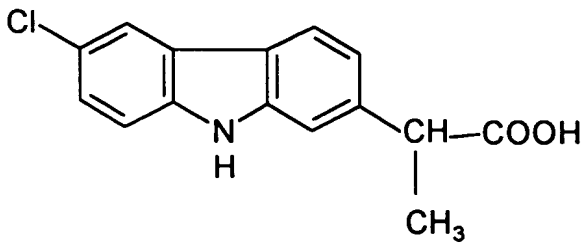
Molecular Weight

273.72

Physical Description

Off-white, odorless crystalline powder; m.p. 197-198°C; soluble in common organic solvents but sparingly soluble in water.

Chemical Formula



(2) RIMADYL was subject to regulatory review under section 512 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §360b).

(3) RIMADYL received permission for commercial marketing or use under section 512 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §360b) on October 25, 1996. It was approved as a non-steroidal antiinflammatory agent for the relief of pain and inflammation in dogs.

(4) The active ingredient in RIMADYL is 6-chloro-∝-methyl-carbazole-2-acetic acid (carprofen). Said active ingredient has not been previously approved for commercial marketing or use

under the Public Health Service Act or the Virus-Serum-Toxin Act. RIMADYL (carprofen) in the form of the (+)-enantiomer was approved for commercial marketing or use as a nonsteroidal antiinflammatory drug (NSAID) in humans under section 505 of the Federal Food, Drug and Cosmetic Act on December 31, 1987.[1] However, the regulatory review period which forms the basis for the present application for extension of the term of United States Patent No. 4,264,500 was not carried out under the same provision of law as that under which the regulatory review period which formed the basis for the approval of RIMADYL (carprofen) for use in humans was carried out. See further Part II, infra.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. §1.720(f). The last day on which this application could be submitted is December 24, 1996.

(6) The patent for which an extension is being sought is identified as follows.

Inventor:	WILLY ZAHLEN
Patent No.:	4,264,500
Title:	PROCESS OF MAKING 6-CHLORO-∝-METHYL-CARBAZOLE-2-ACETIC ACID
Issued:	April 28, 1981
Expires:	February 28, 2000

(7) A copy of United States Patent No. 4,264,500, the patent for which an extension is being sought, is attached hereto as EXHIBIT A.

(8) No disclaimer, certificate of correction, receipt of maintenance fee payment or reexamination certificate has issued in United States Patent No. 4,264,500.

(9) Claims 1-5, all of the claims of United States Patent No. 4,264,500, claim a method of manufacturing the approved

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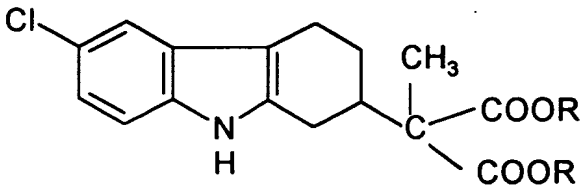
[1] Based on the December 31, 1987 approval of RIMADYL (carprofen) for use in humans, U.S. Patent No. 3,896,145 was extended for a period of two years under 35 U.S.C. §156, pursuant to an application for extension filed by Hoffmann-La Roche Inc. on February 26, 1988.

product. The manner in which each applicable patent claim reads on a method of manufacturing the approved product is as follows.

Claim 1 of U.S. Patent No. 4,264,500 reads as follows.

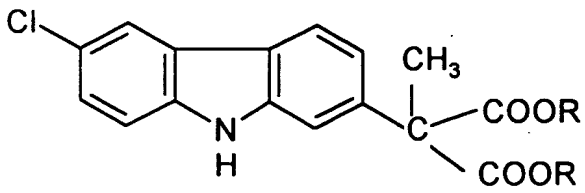
"A process for preparing 6-chloro-α-methyl-carbazole-2-acetic acid, which comprises aromatizing a compound of the formula

I



wherein
R is lower alkyl,
by treatment with chlorine, and therafter [sic] hydrolyzing and decarboxylating the resulting compound of the formula

II



wherein
R is as previously described."

Thus claim 1 claims a process for preparing 6-chloro-α-methyl-carbazole-2-acetic acid, and the latter compound is the active ingredient of RIMADYL (carprofen), the approved product. Therefore, claim 1 reads on a method of manufacturing the approved product.

Claim 2 of U.S. Patent No. 4,264,500 claims the same process as claim 1, except that the scope of the R group in the starting material is restricted to ethyl. Therefore, claim 2 also reads on a method of manufacturing the approved product.

Claim 3 of U.S. Patent No. 4,264,500 claims the same process as claim 1, except that the scope of the R group in the

starting material is restricted to methyl. Therefore claim 3 also reads on a method of manufacturing the approved product.

Claim 4 of U.S. Patent No. 4,264,500 claims the same process as claims 1, 2 and 3, except that the aromatization is restricted to being carried out in an aprotic solvent. Therefore, claim 4 also reads on a method of manufacturing the approved product.

Claim 5 of U.S. Patent No. 4,264,500 claims the same process as claims 1, 2 and 3, except that the aromatization is restricted to being carried out in toluene. Therefore, claim 5 also reads on a method of manufacturing the approved product.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows.

(a) An exemption under subsection (j) of section 512 of the Federal Food, Drug and Cosmetic Act became effective for RIMADYL (carprofen) not later than August 23, 1979, following submission of Investigational New Animal Drug ("INAD") Application No. 2272 on October 18, 1978.[2]

(b) A New Animal Drug Application ("NADA") under section 512 of the Federal Food, Drug and Cosmetic Act for RIMADYL (carprofen) was initially submitted on December 29, 1994, as NADA No. 141-053.

(c) NADA No. 141-053 was approved on October 25, 1996.

In addition, applicant points out that INAD No. 2272 was filed by Hoffmann-La Roche Inc., but that rights under the INAD were transferred by Hoffmann-La Roche Inc. to SmithKline Beecham in November 1993. NADA No. 141-053 was filed by SmithKline Beecham. Rights under both the INAD and the NADA were transferred by SmithKline Beecham to PFIZER INC., the present applicant for patent extension, effective February 2, 1995.

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2 Applicant is unsure of the exact date on which the exemption under subsection 512(j) is considered to have become effective. August 23, 1979 is the date of the first submission to FDA which informed the FDA that the marketing applicant intended to ship drug to an investigator under INAD No. 2272. On this basis, for the purposes of the present application for extension of the term of U.S. Patent No. 4,264,500, applicant requests that August 23, 1979 be considered to be the date on which the exemption first became effective. A copy of the August 23 letter is attached hereto as EXHIBIT B.

(11) A brief description of the significant activities undertaken by or for, or which inure to the benefit of, the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is attached hereto as EXHIBIT C.

(12) Applicant is of the opinion that United States Patent No. 4,264,500 is eligible for an extension under 35 U.S.C. §156, and the length of extension claimed is three (3) years.

The eligibility requirements of 35 U.S.C. §156(a) and (c)(4) have been satisfied as follows.

(a) U.S. Patent No. 4,264,500 claims a method of manufacturing a product, RIMADYL (carprofen).

(b) U.S. Patent No. 4,264,500 is currently set to expire on February 28, 2000 (i.e., the term of the patent has not yet expired).

(c) The term of U.S. Patent No. 4,264,500 has never been extended under subsection (e)(1) of 35 U.S.C. §156.

(d) This application for extension is being submitted by PFIZER INC., the owner of record of U.S. Patent No. 4,264,500, by its agent, in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. §156(d).

(e) The product, RIMADYL (carprofen), has been subject to a regulatory review period under section 512 of the Federal Food, Drug and Cosmetic Act before its commercial marketing or use, and the permission for said commercial marketing or use is the first permitted commercial marketing or use of the product under section 512 of the Federal Food, Drug and Cosmetic Act.

(f) No patent has to this date been extended, nor has any other extension been applied for, under subsection (e)(1) of 35 U.S.C. §156, for the regulatory review period which forms the basis for this application for extension of the term of U.S Patent No. 4,264,500.

The length of extension of the term of U.S. Patent No. 4,264,500 of three (3) years claimed by applicant was determined according to the provisions of 37 C.F.R. §1.778 as follows.

(a) According to 37 C.F.R. §1.778(b), the length of extension is equal to the regulatory review period for the approved product, reduced as appropriate according to paragraphs (d)(1) through (d)(6) of 37 C.F.R. §1.778.

(b) According to 37 C.F.R. §1.778(c), the regulatory review period is the sum of (A) the number of days in the period beginning on the earlier of the date a major health or environmental effects test on the drug was initiated or the date on which an exemption under subsection (j) of section 512 of the Federal Food, Drug and Cosmetic Act became effective for the approved animal drug and ending on the date an application was initially submitted under section 512 of the Federal Food, Drug and Cosmetic Act and (B) the number of days in the period beginning on the date the NADA was initially submitted under subsection (b) of section 512 of the Federal Food, Drug and Cosmetic Act and ending on the date the NADA was approved. The exemption under subsection (j) of section 512 of the Federal Food, Drug and Cosmetic Act became effective on August 23, 1979; the NADA was initially submitted on December 29, 1994; and the NADA was approved on October 25, 1996. Hence, the regulatory review period under 37 C.F.R. §1.778(c) is the sum of the period from August 23, 1979 to December 29, 1994 and from December 30, 1994 to October 25, 1996. This is the sum of 5,606 days and 665 days, which is 6,271 days.

(c) According to 37 C.F.R. §1.778(d)(1)(i), the number of days in the regulatory review period which were on or before the date on which the patent issued must be subtracted. U.S. Patent No. 4,264,500 issued on April 28, 1981. Subtraction of the period on or before April 28, 1981 leaves a reduced regulatory review period which is the sum of the periods from April 29, 1981 to December 29, 1994 and from December 30, 1994 to October 25, 1996. This is the sum of 4,992 days and 665 days, which is 5,657 days.

(d) According to 37 C.F.R. §1.778(d)(1)(ii), the number of days in the regulatory review period during which it is determined by the Secretary of Health and Human Services under 35 U.S.C. §156(d)(2)(b) that applicant was not diligent must be subtracted. In this regard, applicant does not allege that it acted with due

diligence prior to August 12, 1987. Therefore, for the purposes of this application, applicant is further reducing the regulatory review period to the sum of the periods from August 12, 1987 to December 29, 1994 and December 30, 1994 to October 25, 1996. This is the sum of 2,696 days and 665 days, which is 3,361 days.[3]

(e) According to 37 C.F.R. §1.778(d)(1)(iii), the regulatory review period must then be reduced by one-half of the days remaining in the period defined in 37 C.F.R. §1.778(c)(1). This is one-half of 2,696 days, which is 1,348 days. After subtraction, this now leaves a reduced regulatory review period of 2,013 days.

(f) According to 37 C.F.R. §1.778(d)(2), the reduced regulatory review period of 2,013 days must be added to the expiration date of U.S. Patent No. 4,264,500 (February 28, 2000). This gives a date of September 2, 2005. According to 37 C.F.R. §1.778(d)(3), 14 years must be added to the date of approval of the approved product. This gives a date of October 25, 2010. According to 37 C.F.R. §1.778(d)(4), the earlier of these dates must be selected. The earlier date is September 2, 2005.

(g) The provisions of 35 U.S.C. §156(g)(6)(C) and 37 C.F.R. §1.778(d)(6)(ii) apply to this application, because U.S. Patent No. 4,264,500 issued before November 16, 1988 (the date of enactment of the

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[3] At this point, applicant has effectively subtracted from the regulatory review period (i.e., the period extending from the subsection 512(j) exemption date to the approval date of the product), the following periods: (1) the number of days which occurred before the patent issued and (2) the number of days of nondiligence which occurred after the patent issued. This is believed reasonable. If, instead, applicant were to subtract from the regulatory review period (1) the number of days which occurred before the patent isssued and (2) the total number of days of nondiligence which occurred after the filing of the INAD, the reduced regulatory review period at this point would be 1,772 days plus 665 days, which is 2,437 days. If the 1,772-day period were then reduced by one-half, according to 37 C.F.R. §1.778(d)(1)(iii), the reduced regulatory review period would become 886 days plus 665 days, which is 1,551 days. Addition of 1,551 days to the expiration date of U.S. Patent No. 4,264,500 would give a date of May 28, 2004. The 14-year cap date of 37 C.F.R. §1.778(d)(3) would still be October 25, 2010, and the 3-year cap date of 37 C.F.R. §1.778(d)(6)(ii)(A) of February 28, 2003 would still apply. Since the earliest of these three dates is February 28, 2003, applicant would still be entitled to an extension of the term of U.S. Patent No. 4,264,500 until February 28, 2003, i.e., an extension of three (3) years.

Generic Animal Drug and Patent Term Restoration Act), a request for an exemption under subsection (j) of section 512 of the Federal Food, Drug and Cosmetic Act was submitted before November 16, 1988 and the application for commercial marketing or use was not approved before November 16, 1988. Addition of 3 years to the expiration date of U.S. Patent No. 4,264,500 (February 28, 2000), gives a date of February 28, 2003. This date is earlier than September 2, 2005, the date calculated according to 37 C.F.R. §1.778(d)(4). Therefore, applicant is entitled to an extension of term of U.S. Patent No. 4,264,500 until February 28, 2003, i.e., an extension of three (3) years.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the three-year extension being sought to the term of United States Patent No. 4,264,500.

(14) The prescribed fee for receiving and acting on this application for extension is to be charged to Deposit Account No. 16-1445, as requested in the enclosed transmittal letter.

(15) Please address all inquiries and correspondence relating to this application for patent term extension as follows.

J. Trevor Lumb
Pfizer Inc.
Patent Department
235 East 42nd Street
New York, NY 10017-5755

Tel (212) 573-2521
Fax (212) 573-1939

(16) A duplicate of these application papers, certified as such, is enclosed herewith.

(17) A declaration pursuant to 37 C.F.R. §§1.740(a)(17) and 1.740(b) is enclosed herewith.

PART II: THE REQUIREMENTS OF 35 U.S.C. §§156(a)(4)/(a)(5)(A)

35 U.S.C. §156(a)(4) requires that the approved product must have been subject to a regulatory review period before its commercial marketing or use, and §156(a)(5)(A) further requires that "the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred." The present application for patent extension is based on a regulatory review period for the chemical entity carprofen, as an a new animal drug, under section 512 of the Federal Food, Drug and Cosmetic Act. Although carprofen, as its (+)-enantiomer, was approved for commercial marketing or use in humans, as a nonsteroidal antiinflammatory agent, on December 31, 1987, carprofen was approved for use in humans after a regulatory review period under section 505 of the Federal Food, Drug and Cosmetic Act. Since section 512 regulates only new animal drugs, while section 505 regulates only new human drugs, these two approvals were carried out under two different provisions of law. Therefore, the regulatory review period which forms the basis of this application for patent term extension was the first approval under the provision of law (section 512 of the Federal Food, and Drug Act) under which it took place. Under these circumstances, the eligibility requirements of 35 U.S.C. §§156(a)(4)/156(a)(5)(A) have been satisfied.

Support for the fact that the term "provision of law" in 35 U.S.C. §156(a)(5)(a) means just the individual statutory sections covering approval of carprofen as a new animal health product, rather than the totality of the Federal Food, Drug and Cosmetic Act, is found, inter alia, in the language of the Supreme Court in Eli Lilly and Co. v. Medtronic Inc., 15 U.S.P.Q.2d 1121 (1990). In Lilly, in concluding that the phrase "a Federal law which regulates the manufacture, use or sale of drugs" in 35 U.S.C. §271(e)(1) means the entire Federal Food, Drug and Cosmetic Act, rather than merely those sections that relate to drugs, the Court contrasted the language of section 271(e)(1) with the language of 35 U.S.C.

156(a)(5)(A). Specifically, the Court concluded that, the "section of the 1984 Act [35 U.S.C. §156(a)(5)(A)], when it meant to refer to a particular provision of law rather than an entire Act, referred to 'the first permitted commercial marketing or use of the product under the provision of law.'" Id. at 1125 (emphasis in original).

Moreover, the conclusion that sections 505 and 512 are separate provisions of law is evidenced by the fact that they were enacted at different times to serve different needs. Regulatory reviews of new human drugs and new animal drugs are carried out differently by the FDA. They are handled by different entities within the FDA (Center for Drug Evaluation and Research for human products; Center for Veterinary Medicine for animal products), and the approval processes involve different testing methods and criteria for approval. The approvals are governed by separate sections of the Code of Federal Regulations (21 C.F.R. §200 et seq. for human drugs; 21 C.F.R. §500 et seq. for animal drugs).

Yet further, the manner in which Congress has legislated patent term extension indicates that it considers that new human drugs and new animal drugs are approved by the FDA under different provisions of law. In 1984, when Congress enacted the Hatch-Waxman Act (Drug Price Competition and Patent Term Restoration Act of 1984) it introduced abbreviated new drug applications, patent term extension and marketing exclusivity periods, and it partially overruled Roche v. Bolar. But it did so only for human drugs. Thus, Congress clearly envisaged that the provisions of the Federal Food, Drug and Cosmetic Act which dealt with new human drugs were different from those regulating new animal drugs. Indeed, at the time carprofen was approved for use in humans (December 1987), it was not possible to obtain patent term extension for patents covering animal health products. Only in 1988, with passage of the Generic Animal Drug and Patent Term Restoration Act, did it become possible to extend the term of patents covering animal health products.

Based on the foregoing, applicant respectfully submits that it is entitled to an extension of the term of U.S. Patent No 4.264,500 of three (3) years.

Respectfully submitted,
PFIZER INC.

Date: December 20, 1996

By: J. Trevor Lumb

J. Trevor Lumb
Reg. No. 28,567
Tel.: (212) 573-2521

Pfizer Inc.
Patent Department
235 East 42nd Street
New York, NY 10017-5755

EXHIBIT A

United States Patent [19]

Zwahlen

[11] **4,264,500**

[45] **Apr. 28, 1981**

[54] **PROCESS OF MAKING 6-CHLORO-α-METHYL-CARBAZOLE-2-ACETIC ACID**

[75] Inventor: **Willy Zwahlen**, Thürnen, Switzerland

[73] Assignee: **Hoffmann-La Roche Inc.**, Nutley, N.J.

[21] Appl. No.: **125,529**

[22] Filed: **Feb. 28, 1980**

[30] **Foreign Application Priority Data**

Mar. 2, 1979 [CH] Switzerland 2104/79

[51] **Int. Cl.**[3] **C07D 209/82**

[52] **U.S. Cl.** **260/315**

[58] **Field of Search** 260/315

[56] **References Cited**

U.S. PATENT DOCUMENTS

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4,158,007	6/1979	Gurien et al.	260/315

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Derwent 62340T, (5–2–1971), Japanese Pat. Publication 4,717,760.

Derwent 33801W, (17–11–1972), Russian Patent 437,770.

Primary Examiner—Henry R. Jiles

Assistant Examiner—R. W. Ramsuer

Attorney, Agent, or Firm—Jon S. Saxe; Bernard S. Leon; William G. Isgro

[57] **ABSTRACT**

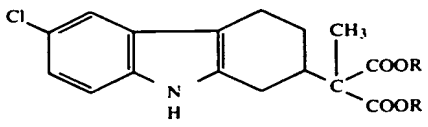
The aromatization of (6-chloro-1,2,3,4-tetrahydro-2-carbazolyl)-methyl-malonic acid dialkyl ester, utilizing chlorine and subsequent conversion of the resulting product to 6-chloro-α-methyl-carbazole-2-acetic acid by hydrolysis and decarboxylation are described.

5 Claims, No Drawings

PROCESS OF MAKING 6-CHLORO-α-METHYL-CARBAZOLE-2-ACETIC ACID

BRIEF SUMMARY OF THE INVENTION

The invention relates to the aromatization of a compound of the formula

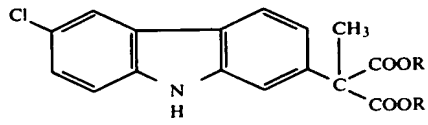


I

wherein

R is lower alkyl,

by treatment with chlorine and subsequent hydrolysis and decarboxylation of the resulting compound of the formula



II

wherein

R is as previously described,

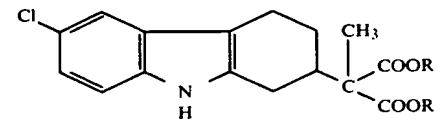
to yield 6-chloro-α-methyl-carbazole-2-acetic acid.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to a process for the preparation of 6-chloro-α-methyl-carbazole-2-acetic acid, which is known for its pharmaceutical properties.

6-Chloro-α-methyl-carbazole-2-acetic acid has been prepared by treating 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester with an aromatizing agent, such as, p-chloranil and subsequently hydrolyzing the resulting 6-chloro-α-methyl- carbazole-2-acetic acid ethyl ester. A disadvantage of this known process is the use of aromatizing agents such as p-chloranil which lead to the formation of undesired by-products, especially of chlorine-containing by-products which are difficult to use. Another disadvantage of this process comprises the fact that the aromatizing agent cannot be removed directly and can be regenerated only in an expensive manner.

In accordance with the invention, there is provided a process by which 6-chloro-α-methyl-carbazole-2-acetic acid can be prepared in high yield and without the aforementioned disadvantages. The process provided by the present invention comprises aromatizing a compound of the formula

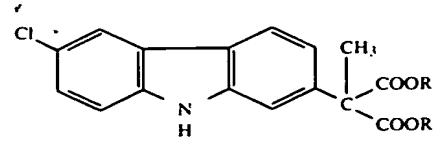


I

wherein

R is lower alkyl,

by treatment with chlorine and hydrolyzing and decarboxylating the resulting compound of the formula



II

wherein

R is as previously described.

The lower alkyl group denoted by R in formulas I and II hereinbefore can be branched-chain or, preferably, straight-chain. Examples of such lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, and the like; methyl and especially ethyl are preferred.

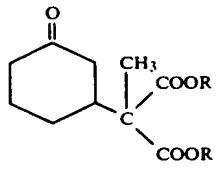
The aromatization of a compound of formula I is conveniently carried out in an aprotic solvent such as toluene, methylene chloride or ethylene chloride, preferably toluene, at an elevated temperature, especially up to the reflux temperature of the mixture, while slowly adding chlorine. Preferably, chlorine is added within about 2 to 8 hours, preferably over a period of about 4 hours. When methylene chloride is used as the solvent the aromatizaton is conveniently carried out at about 40° C. and when toluene is used as the solvent the aromatization is conveniently carried out at a temperature in the range of from about 50° C. to the reflux temperature of the mixture, preferably at about 75° C.

The compounds of formula II can be isolated from the mixture in a known manner, for example, by crystallization, or can be subjected in situ to the subsequent step of the process.

The hydrolysis and decarboxylation of a compound of formula II can be carried out simultaneously in a known manner by treatment with acids, for example, by means of glacial acetic acid in the presence of a hydrohalic acid, such as, hydrochloric acid.

The process provided by the present invention can be carried out batchwise or, preferably, continuously.

The starting materials of formula I can be obtained by reacting an α-methyl-3-oxocyclohexane-malonic acid di(lower alkyl) ester of the formula



III

wherein

R is as previously described,

with p-chlorophenylhydrazine, conveniently in an inert organic solvent, for example, an alkanol, such as, ethanol, at a temperature in the range of from about 25° C. to 100° C., preferably at room temperature.

The Examples which follow further illustrate the invention. All temperatures are stated in degrees Centigrade, unless otherwise mentioned.

EXAMPLE I

Preparation of 6-chloro-α-methyl-carbazole-2-acetic acid

2.5 Kg. of (6-chloro-1,2,3,4-tetrahydro-2-carbazolyl)-methyl-malonic acid diethyl ester are introduced into a 100 liter reaction vessel and 75 liters of toluene are added. The mixture is heated to 75° C. with stirring and

the vessel is evacuated to −0.6 bar. 940 G. of chlorine gas are passed in slowly within 4 hours.

The solution is cooled to 20° C. 10 Liters of deionized water are added. The pH of the aqueous phase is adjusted to 8–9 with 1.25 kg. of sodium bicarbonate and the aqueous phase is separated. 10 Liters of deionized water are added to the toluene phase, the mixture is stirred and the aqueous phase is separated. The combined aqueous phases are extracted with 15 liters of methylene chloride. The methylene chloride phase is evaporated in vacuo, the toluene phase is added and the mixture is concentrated to a volume of 5 liters in vacuo. It is then cooled to 0° C. and stirred at this temperature overnight. The product is removed by filtration under suction and washed with 1 liter of toluene. After drying overnight in vacuo at 60° C., there are obtained 2.1 kg. (85% of theory) of (6-chloro-2-carbazolyl)-methyl-malonic acid diethyl ester having a melting point of 134°–136° C.

The mother liquors from several batches are concentrated to 1/10 of their volume. After crystallization, there are obtained an additional 170 g. (6.8%) of product per batch.

A mixture of 247 g. of (6-chloro-2-carbazolyl)-methyl-malonic acid diethyl ester, 1.9 liters of glacial acetic acid and 1.9 liters of 6 N hydrochloric acid is heated under reflux overnight with stirring and the resulting black solution is cooled to room temperature. The solid formed is removed by filtration, washed with acetic acid/water (1:1) and water and then dried. The 192 g. of crude 6-chloro-α-methyl-carbazole-2-acetic acid obtained are dissolved in 1.2 liters of 1 N potassium hydroxide, the solution is extracted with four 300 ml. portions of diethyl ether and acidified by the addition of 100 ml. of concentrated hydrochloric acid while cooling in an ice-bath under nitrogen. The mixture is stirred for 15 minutes, the precipitated solid is removed by filtration, washed with water and dried. 167.7 G. of product are obtained. The last purification is carried out by crystallization from 4.7 liters of boiling 1,2-dichloroethane with 8.0 g. of active carbon. The solution is cooled overnight, the crystals are removed by filtration, washed with dichloroethane and dried. There are obtained 103.8 g. (57.3% of theory) of almost white 6-chloro-α-methyl-carbazole-2-acetic acid having a melting point of 198.5°–201° C.

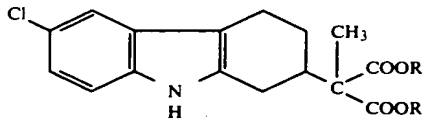
The (6-chloro-1,2,3,4-tetrahydro-2-carbazolyl)-methyl-malonic acid diethyl ester used as the starting material can be prepared as follows:

2.5 G. of sodium are added to 325 ml. of ethanol, the solution is treated within 5 minutes with 200 g. of methyl-malonic acid diethyl ester and the mixture is stirred for 1 hour. A solution of 100 g. of 2-cyclohexan-1-one in 130 ml. of ethanol is then added within a one hour period. The resulting mixture is stirred overnight. After the addition of 20 ml. of acetic acid, the mixture is evaporated, the resulting oil is dissolved in 1.31 liters of diethyl ether and the solution is washed with water. The ethereal solution is dried, filtered and again dried. Thereafter, the ether is removed under reduced pressure and the residual oil is distilled in vacuo. There are obtained 211.5 g (75.4% of theory) of α-methyl-3-oxocyclohexane-malonic acid diethyl ester having a boiling point of 129°–130° C./0.2.

A mixture of 100 g. of α-methyl-3-oxocyclohexane-malonic acid diethyl ester, 66.3 g. of p-chlorophenyl-hydrazine hydrochloride and 300 ml. of ethanol is stirred for 1.5 hours and then heated under reflux for 1.5 hours. The mixture is left to stand at room temperature overnight. Then, it is cooled in an ice-bath and the crystals are removed by filtration. The filter cake is dried, washed with ice-cold ethanol and then with hexane/ethanol (1:1) and dried. The 91.7 g. of solid obtained are stirred with 50 ml. of water in an ice-bath under nitrogen, filtered, washed with water and dried. There are obtained 78.8 g. (56.5% of theory) of (6-chloro-1,2,3,4-tetrahydro-2-carbazolyl)-methyl-malonic acid diethyl ester having a melting point of 129°–130° C.

I claim:

1. A process for preparing 6-chloro-α-methyl-carbazole-2-acetic acid, which comprises aromatizing a compound of the formula

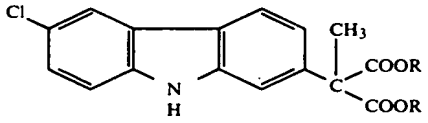


I

wherein

R is lower alkyl,

by treatment with chlorine, and therafter hydrolyzing and decarboxylating the resulting compound of the formula



II

wherein

R is as previously described.

2. A process in accordance with claim 1, wherein a compound of formula I wherein R is ethyl is utilized.

3. A process in accordance with claim 1, wherein a compound of formula I where R is methyl is utilized.

4. A process in accordance with claims 1, 2 or 3, wherein the aromatization is carried out in an aprotic solvent.

5. A process in accordance with claims 1, 2 or 3, wherein the aprotic solvent is toluene.

* * * * *

EXHIBIT B R93 1345

HOFFMANN-LA ROCHE INC. AH0004

NUTLEY · NEW JERSEY 07110 · TELEPHONE (201) 235-5000 · (N.Y.C.) 695-1400

RESEARCH DIVISION

DATE August 23, 1979
INAD 2272
Name of Drug Ro 20-5720 in dogs
TRIAL NO. C-20-A

Office for Scientific Evaluation
Division of Drugs for Non-Food Animals - HFV-114
Bureau of Veterinary Medicine
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

The sponsor, Hoffmann-La Roche Inc., submits the attached notice of claimed investigational exemption for Ro 20-5720 under the provisions of Section 512 of the Federal Food, Drug and Cosmetic Act and Title 21, Section 511.1b of the Code of Federal Regulations.

In the attached submission the pages are marked "CONFIDENTIAL" because the materials on the pages constitute trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). If, for any reason, Food and Drug Administration officials should feel that disclosure of any of the materials marked "CONFIDENTIAL" should be made to any member of the public, we expect that because of the importance of maintaining secrecy of these materials to Hoffmann-La Roche Inc. you will first consult with us on the issue of disclosure.

Sincerely,

HOFFMANN-LA ROCHE INC.

Raymond E. McKinley, V.M.D.
Assistant Director
Animal Health Research

REM/ja
HLR No. 20479

DATE August 23, 1979
INAD NO. 2272
NAME OF DRUG Ro 20-5720 in dogs
TRIAL NO. C-20-A

Date of Drug Shipment: As soon as possible

Name of Investigator: Dr. Alan M. Farber
Associate Director of Clinics

Address of Investigator: Henry Bergh Memorial Hospital of ASPCA
441 East 92nd. Street
New York, New York 10028

Approximate number of animals: 100 dogs

Approximate Starting Date: As soon as possible

Species of animals: canine

Maximum daily dose: 5 mg/kg

Method of Administration: oral

If this investigation is discontinued, the Food and Drug Administration will be notified, giving the reason for discontinuance and disposition of the drug.

CONFIDENTIAL

EXHIBIT C

BRIEF DESCRIPTION OF REPRESENTATIVE
SIGNIFICANT ACTIVITIES DURING THE
REGULATORY REVIEW PERIOD FOR RIMADYL (CARPROFEN)

(For explanation of abbreviations, see last page of Exhibit C)

DATE	ACTIVITY	COMMENTS
10/18/78	Submission to CVM	Initial INAD submission.
10/30/78	Letter from CVM	Acknowledgement of 10/18/78 submission. Assignment of INAD No. 2272.
11/16/78	Letter from CVM	Offer to arrange conference to discuss protocol development.
08/23/79	Submissions to CVM	NODS - Trials C-20-A, C-26, C-20-B and C-20-C.
07/08/80	Submission to CVM	Notification of termination of Trial C-20-A.
08/07/80	Submission to CVM	NODS - Trial C-20-D.
10/30/80	Submission to CVM	Proposed protocol for evaluation of carprofen.
01/08/81 02/02/81	Telecons	Discussed status of FDA review of the proposed protocol.
03/02/81	Letter from CVM	Comments on the proposed protocol.
10/14/81	Submission to CVM	Amended protocol.
01/18/82	Letter from CVM	Comments on the amended protocol.
08/12/87	Internal memorandum of applicant	Summarized recent meetings with FDA re plans for further trials. Meeting to be scheduled with FDA re requirements and methodology for NADA submission.
08/19/87	Submission to CVM	NODS - Trial C-87-36.
11/05/87	Letter from CVM	Requested additional information before drug shipments.
12/01/87	Submission to CVM	Additional information about Trial C-87-36.
01/28/88	Submissions to CVM	NODS - Trials C-88-3, C-88-6 and C-88-8.
04/25/88 06/07/88	Letters from CVM	Requested additional information about Trials C-88-3, C-88-6 and C-88-8. Requested report on past studies.
06/22/88	Submission to CVM	Report on past studies of carprofen in dogs.
08/22/88	Letter from CVM	Request for draft protocols; request for accounting of 240 dogs used in the INAD.
09/19/88	Submission to CVM	Response to 08/22/88 letter from CVM.
12/02/88	Letter from CVM	Confirmation that 09/19/88 response was satisfactory.
02/17/89	Submission to CVM	Confirmation of 03/10/89 meeting re use of computer enhanced gait analysis program as model to evaluate carprofen. Information was attached to submission.
05/25/89	Submission to CVM	Protocol OST 2272-2 for dose titration study for use in osteoarthritis in dogs.
08/28/89	Letter from CVM	Comments on OST 2272-2 protocol.
10/02/89	Submission to CVM	Updated OST 2272-2 protocol and Technical Data Sheet
10/30/89	Submission to CVM	Protocol 2272-3 for blinded efficacy study.

11/02/89	Submissions to CVM	Report N-30191 on one-year oral toxicity study; Protocol Study 05366 concerning bioequivalency study in dogs with carprofen.
02/05/90	Submissions to CVM	NODS - Trials C-89-44 and C-90-7. Protocol 2272-5 for non-blinded safety study. Documentation to support SID dosage rather than BID dosage in response to 01/26/90 telephone request from FDA.
05/06/90	Submission to CVM	Request for "Expedited Review" status (Type 1A drug classification).
05/16/90	Letters from CVM	Comments on protocol for controlled clinical trials in university setting and one-year toxicity study; notice that abbreviated EA required prior to NADA approval; request for additional information re SID dosing and effect of food on bioavailability.
05/21/90	Submissions to CVM	NODS - Trials C-90-23, C-89-44, C-90-7, C-90-38, C-90-50, C-90-42, C-90-41, C-90-43, C-90-44, C-90-40, C-90-62, C-90-63, C-90-64, C-90-52, C-90-53, C-90-54, C-90-55 and C-90-56.
06/19/90	Submissions to CVM	Report 24036 re oral toxicity study in dogs. Report 30985 re blood level study in dogs during chronic tolerance-toxicity evaluation of carprofen in dogs..
08/23/90	Submissions to CVM	Protocols 2272-6, 2272-7 and 2272-8; changes to study protocol 2272-2..
08/24/90	Letter from CVM	Request for expedited review status denied.
09/11/90	Submission to CVM	Response to FDA comments on protocols 2272-6, 2272-7 and 2272-8.
10/02/90	Submission to CVM	Response to FDA comments on recently submitted toxicology report and Report N-122487.
10/26/90 01/10/91	Submissions to CVM	NODS - Trials C-90-20, C-90-56, C-90-52, C-90-53, C-91-1, C-91-2, C-91-3, C90-38, C-90-57, C-90-54 and C-90-50.
01/21/91	Submission to CVM	Type I Master File to facilitate review of Type II Master File for synthesis of carbazole ester.
02/08/91	Letters from CVM	Comments re one-year dog toxicity study; request to refrain from shipping drug for Trial C-90-74 until FDA has reviewed it further; comments on protocols 2272-6, 2272-7 and 2272-8 and requests for changes.
03/11/91	Submission to CVM	Updated protocols 2272-6, 2272-7 and 2272-8.
04/03/91 05/01/91	Submissions to CVM	NODS - Trials C-91-34, C-90-52, C-90-53, C-91-37, C-90-54, C-91-25, C-90-59. C-90-58, C-90-60, C-90-50, C-91-45, C-91-46, C-90-56, C-90-57, C-91-36, C-90-54, C-91-48, C-91-49, C-91-50, C-91-51, C-90-48, C-90-62, C-91-55, C-91-54, C-91-53, C-91-57, C-91-58, C-91-59, C-91-60, C-91-61, C-91-62, C-91-63 and C-91-64.
06/11/91	Submissions to CVM	Change to Study 2272-6 for Trials C-90-62, C-90-63, C-90-64, C-91-26, C-91-33 and C-91-34. Third randomization table for study C-90-40, protocol 2272-6.

07/08/91	Submission to CVM	Phased data submission: report N-127594 (dose titration study).
08/05/91 09/04/91	Submissions to CVM	NODS- Trials C-90-54, C-90-56, C-91-54, C-91-74, C-91-75, C-91-76, C-91-72, C-90-52, C-91-67, C-91-1, C-91-79, C-90-60, C-90-52, C-91-37, C-90-53, C-90-57, C-91-73, C-91-29, C-91-54, C-90-41, C-91-46 and C-91-63.
10/11/91	Submission to CVM	Revised target animal safety and drug tolerance protocol (Study No. 05966).
10/25/91	Telecon	Discussed phased submission of carprofen NADA, composition and manufacturing/chemistry sections.
10/30/91 12/19/91	Letters from CVM	Numerous requests to justify amount of drug shipped.
11/08/91 12/18/91	Submissions to CVM	NODS - Trials C-91-45, C-91-54, C-90-52, C-91-72, C-91-83, C-91-49, C-91-61, C-91-88, C-91-87, C-91-85, C-91-37, C-91-79, C-90-60, C-91-92 and C-90-54.
01/22/92	Submission to CVM	Type II Master File for synthesis of carbazole ester (VMF-5395).
01/28/92	Letter from CVM	Acknowledged receipt of VMF-5395 sent 01/22/92.
02/03/92	Submissions to CVM	Phased Data Submission: Index; components and composition; manufacturing methods facilities and controls; samples.
02/14/92	Submissions to CVM	Phased Data Submissions - clinical studies (18 volumes).
02/19/92	Submission to CVM	Interim report on extended use of carprofen.
02/20/92	Submission to CVM	Phased Data Submission: Target Animal Safety and Drug Tolerance Studies; Index; Summary of Report N-127794; Table of Contents; Abstact & Summary; Material and Methods; Results and Conclusions; Figures & Tables; Appendices.
02/24/92	Submission to CVM	Request for Expedited Review status (resubmission).
03/02/92 04/03/92 05/13/92	Submissions to CVM	NODS - Trials C-91-58, C-91-54, C-91-37, C-91-87, C-90-57, C-91-83, C-91-64, C-91-73, C-90-58, C-91-75, C-90-54, C-90-56, C-91-67, C-90-52, C-91-29, C-91-73, C-91-45 and C-90-53.
05/25/92	Letter from CVM	Comments on report submitted 02/19/92. Applicant has adequately addressed request for interim update.
06/10/92	Submissions to CVM	NODS - Trials C-91-25, C-90-53, C-91-87, C-90-50, C-92-18, C-91-61, C-91-58 and C-91-29.
07/02/92 08/27/92	Submissions to CVM	NODS - Trials C-90-57, C-91-46, C-90-52, C-90-56, C-90-54, C-90-53, C-91-83, C-90-58, C-91-87, C-92-21, C-92-8, C-92-20, C-91-49, C-91-73 C-91-57, C-91-29, C-91-75 and C-91-37; letter updating status of extended (compassionate) use in dogs.
08/18/92	Letter from CVM	Asked for justification of amount of drug shipped to, and number of dogs to be treated for, several studies; and for interim report on pivotal studies to support continued extended use under protocol 2272-8.

09/02/92	Submissions to CVM	NODS - Trials C-90-54, C-91-64, C-91-51, C-92-20, C-91-61, C-90-52, C-91-87, C-91-67, C-91-58, C-90-56, C-91-25, C-91-83, C-91-53, C-90-57 and C-90-53.
09/04/92	Letters from CVM	Requested justification of amount of drug shipped to investigators for several studies.
10/19/92 11/11/92	Submissions to CVM	NODS - Trials C-92-8, C-91-1, C-90-54, C-91-46, C-91-52, C-90-50, C-90-52, C-90-53, C-90-57, C-91-29 and C-91-83.
10/23/92 11/23/92	Letters from CVM	Query re amount of drug shipped for several studies; request for interim report on non-pivotal studies and for support for continued extended studies under 2272-8.
12/17/96	Submissions to CVM	NODS - Trials C-90-56 and C-90-54.
01/12/93	Submissions to CVM	Interim report in response to 11/23/92 letter from FDA; summary of the number of dogs that are or have been on extended trial.
02/05/93	Letter from CVM	Referred to submission dated 08/19/92; FDA stated that it cannot determine an effective dose and dosing regimen from the data provided.
03/01/93	Letter to CVM	Confirming meeting scheduled for 03/11/93.
04/12/93	Letter to CVM	Follow-up to meeting of 03/11/93 regarding carprofen dose titration study.
04/13/93 05/04/93	Submissions to CVM	NODS - Trials C-99-54, C-91-83, C-91-67, C-90-54, C-91-64 and C-90-56.
05/26/93	Submission to CVM	VMF 5395, Master File for synthesis of carbazole ester.
06/18/93	Telecon	Discused status of carprofen dose titration review.
07/14/93	Letter from CVM	Comments on letters dated 03/01/93 and 04/12/93.
08/23/93	Letter from CVM	Comments on Master File 5394, submitted 05/26/93.
09/09/93	Submissions to CVM	NODS - Trials C-91-57, C-90-53, C-90-56, C-91-75, C-90-50, C-90-52, C-91-61 and C-91-53.
10/14/93	Submissions to CVM	NODS - Trials C-90-53, C-90-58 and C-91-25.
11/15/93	Letters to FDA	Informed FDA that Hoffmann-La Roche had transferred INAD No. 2272 to SmithKline Beecham Corporation.
12/16/93	Letter from CVM	Division of Therapeutic Drugs, Non-Food Animals, accepts transfer of INAD No. 2272 to SmithKline Beecham from Hoffmann-La Roche.
12/17/93 12/21/93	Submissions to CVM	Additional data regarding dose titration, target animal safety submission of 02/20/92, blood plasma concentration studies, etc.
02/28/94	Telecons	Discussed status of two submissions: dose titration and blood plasma levels. Discussed manufacturing and chemistry sections.
03/14/94	Submission to CVM	Explanation of importation of Zenecarb (injectable formulation of carprofen) as requested by Dr. Wilmot.
04/01/94	Submission to CVM	Disk descriptions alnd data file listings for carprofen clinical efficacy studies with corresponding diskettes; stated that diskettes with target animal safety data will be forwarded when received from Hoffmann-La Roche.

04/12/94	Letter from CVM	Requests target animal safety study variables on data disk; includes list of variables which are crucial to review of study.
05/04/94	Submissions to CVM	Corrected diskette and hard copy of efficacy data; report of discrepancies between NADA data and data diskettes for certain studies.
06/17/94	Letters from CVM	Comments on target animal safety; CVM informed applicant that plasma concentration data will not be reviewed until receipt of safety data on diskette; comments on dose titration studies.
07/20/94	Submissions to CVM	Diskette with actual raw data from dog study 05966; explanation of discrepancies between clinical signs data provided by Hoffmann-La Roche to SmithKline Beecham and data submitted to FDA.
08/02/94	Submissions to CVM	Target animal safety study variables and raw data requested by CVM 04/12/94 in hard copy and on diskette; further explanations re discrepancies.
09/09/94 09/12/94	Telecons	Discussions re evaluation of results from several studies; CVM stated that lack of plasma concentration data in electronic form will slow the review.
09/23/94	Inter-company transfer of information	Hoffmann-La Roche sent diskettes with RS1 tables for target animal safety study in .ZIP, .EXE and ASCII files to SmithKline Beecham.
10/05/94	Submissions to CVM	Submissions by Leiras Oy (bulk drug manufacturer) re VMF-5521 (carbazole ester new drug substance) and VMF-5520 (carprofen new drug substance).
11/01/94	Submission to CVM	Response to CVM letter of 10/12/94 concerning study of carprofen by Dr. Ann Johnson in a university setting.
12/06/94	Letter from FDA to an investigator	Form 483 issued to Dr. Shapiro regarding inspection of carprofen pivotal dose determination study, C-89-44.
12/07/94	Letter from CVM	Comments and minutes of 09/01/94 carprofen dose confirmation meeting.
12/23/94	Submission to CVM	Carprofen Force Plate Data Disks and a directory listing; diskettes with raw data from university clinical study.
12/29/94	Submission to CVM	NADA filed.
01/03/95	Letter from CVM	Acknowledgment of NADA submission. Assignment of NADA No. 141-053.
01/12/95	Telecon	Discussed Form 483 issued to Dr. Shapiro (concerns re carprofen pivotal dose determination study). CVM indicated that there would be no delay in FDA review.
01/30/95	Letter from CVM	Comments on VMF-5520 and VMF-5521.
02/02/95	Submission to CVM	Informed FDA about acquisition by Pfizer Inc. from SmithKline Beecham Corporation of INAD No 2272 and NADA No. 141-053 on 01/19/95.
03/08/95	Telecon	Re carprofen pivotal clinical studies; CVM requested breakdown of dogs within certain weight ranges.
03/20/95	Submission to CVM	Revised efficacy data; two pivotal clinical efficacy studies on diskettes.

04/12/95	Telecon	Discussed: updated EA; status of new facility; manufacture of bulk drug.
05/02/95	Submission to CVM	Submission by Leiras Oy (bulk manufacturer) re VMF-5520 for carbazole ester and VMF-5521 for carprofen.
06/08/95	Submission to CVM	Response to FDA 483 (Dr. Shapiro, study C-89-44).
07/10/95	Telecon	Re status of NADA; CVM indicated that an incomplete letter will be issued.
08/04/95	Letter from CVM	Incomplete letter; explanation of FDA's concerns.
12/21/95	Letter to CVM	Confirms meeting for 01/18/96. Objective of meeting is to discuss efficacy , safety, labeling and FOI summary.
01/19/96	Letter to CVM	Rescheduling of meeting to 01/23/96.
01/24/96	Telecon	Discussed use of registered trademark symbol in labeling.
04/26/96	Letter from CVM	Memorandum of conference for 01/23/96 meeting.
05/09/96	Submission to CVM	Detailed response to CVM's letter of 08/04/95.
05/31/96	Submission to CVM	Electronic Data Files/FOI Summary. Updated files.
06/07/96 06/12/96	Telecons	Re Hoffmann-La Roche Pre-Approval Inspection.
06/21/96 to 07/25/96	Numerous Telecons and one fax (06/27/96)	FOI summary/package insert/labeling.
08/14/96	Submissions to CVM	Discussed labeling and FOI Summary.
09/11/96 09/12/96 09/13/96	Telecons	Discussed labeling and CMC.
10/09/96	Letter to CVM	Revised facsimile package insert and bottle labeling.
10/22/96	Telecon	Discussed labeling.
10/25/96	Letter from FDA	Approval of NADA No. 141-053.

EXPLANATION OF ABBREVIATIONS

CVM	Center for Veterinary Medicine
INAD	Investigational New Animal Drug
NADA	New Animal Drug Application
NODS	Notice of Drug Shipment
Telecon	Telephone Conversation between Applicant and FDA
VMF	Veterinary Master File
EA	Environmental Assessment
RSI	Computer Program for Statistical Analysis of Data
Form 483	Form used by FDA for reporting procedural deficiencies following an inspection of an investigator
CMC	Chemistry Manufacturing and Controls